In re application of
Evans et al.
Application No. 09/526,298

PATENT
Atty. Dckt. No. P41-9321 (SALK1320-3)
(088802-1103)

Please cancel claims 49-53 without prejudice to their future prosecution.

REMARKS

The present invention relates to methods for modulating the expression of a gene in a subject that contains one or more cells comprising: a gene of interest under the control of a steroid or steroid-like hormone response element; an ultraspiracle receptor; and a receptor that, in the presence of its cognate ligand and the ultraspiracle receptor, binds to the steroid or steroid-like hormone response element. By contacting such cells with the cognate ligand, the expression of the gene of interest can be modulated.

Claims 14-19 and 35-53 are currently pending in the instant application, with claims 49-53 having been withdrawn from consideration by restriction requirement. Applicants have cancelled claims 49-53 herein. For the convenience of the Examiner, a copy of the pending claims, reflecting this amendment, are submitted herewith as Appendix A.

35 U.S.C § 112, First Paragraph

The rejection of claims 14-19 and 35-48 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that the specification does not enable the skilled artisan to use the invention commensurate with the scope of the claims.

The standard for determining enablement is whether the specification as filed provides sufficient information as to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

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Applicants respectfully disagree with the Examiner's continued contention that the instant specification does not meet the enablement standard. It is respectfully submitted that the Examiner's contention is based on a flawed interpretation of the instant claims. Furthermore, when the claims are properly interpreted, it is clear that the claims meet the enablement standard of 35 U.S.C. § 112, first paragraph.

The instant claims relate to methods for modulating gene expression in subjects that contain a DNA construct encoding an exogenous gene under control of a hormone response element, a receptor that, when bound to ultraspiracle receptor and a ligand, binds to the hormone response element, and ultraspiracle receptor. Applicants respectfully submit that the Examiner has ignored the plain language of the claims, and erroneously asserted that the instantly claimed methods are "drawn to nucleic acid based therapy" (Paper No. 9, paragraph bridging pages 2 and 3), despite the fact that the phrase "nucleic acid based therapy" does not appear in the claims. Similarly, the Examiner has erroneously asserted that the claims "involve methods of introducing and expressing exogenous genes and nucleic acid sequences in specific cells in a whole animal" (Paper No. 9, page 3) despite the fact that the claims do not require methods in which specific cells comprise exogenous genes.

The flaws in the Examiner's interpretation of the claims are further highlighted by the Examiner's discussion in Paper No. 9, page 3, as to why the instant claims allegedly fail to satisfy the enablement requirement:

> For example, the instant specification fails to teach one of skill in the art how to integrate the gene construct for the exogenous ultraspiracle receptor to specific desired cells such that expression would be at a level adequate for inducing the expression of a gene under the appropriate hormone response element. The targeting of specific cells would be required, for example in cases where as applicant contemplates and claims, a method of selectively killing cells and for directing expression of a desired gene in a specific cell type or tissue type.

In fact, the instant claims never require that a gene construct be integrated into specific cells, or refer to "selectively killing cells" or "expression of a desired gene in a specific cell type

or tissue type." While Applicants disagree that the specification as filed fails to enable the methods to which the Examiner refers, Applicants respectfully submit that the Examiner's statement is not relevant to the instant claims.

Thus, contrary to the Examiner's assertions in Paper No. 9, page 3, the instant claims are not directed to nucleic acid therapy *per se*, but to any of a number of possible applications based on the realization that gene expression can be modulated using a receptor that, in the presence of the ultraspiracle receptor and a ligand, binds to hormone response elements. Nor, contrary to the Examiner's assertions, are the claims directed to introducing nucleic acid sequences into specific cells in a whole animal. Rather, the skilled artisan will understand that, for example, *ex vivo* strategies can be used to provide DNA constructs useful for carrying out the instantly claimed methods; *i.e.*, methods in which DNA constructs can be inserted into cells, *e.g.*, in culture, and the resulting cells introduced into subjects for various purposes, including therapeutic purposes. *See, e.g.*, specification, page 19, lines 29-35, and page 21, lines 23-28; *see also*, R.G. Crystal, *Science* 270: 404-410 (1995), Table 2 (describing successful *ex vivo* gene therapy strategies).

Accordingly, in response to the Examiner's statement that "[i]t is unclear how the interpretation [of the claims] is to[o] narrow" (Paper No. 9, page 5), Applicants respectfully submit that the Examiner's interpretation of the claims is improper and overly narrow because the Examiner includes elements that are not present in the claims, and rejects the claims based on these improperly included elements. *See*, MPEP §2111.01 (importing limitations not present in the claims is not a reasonable claim interpretation).

Moreover, when the claims are properly interpreted, it is clear that the instant claims meet the enablement standard of 35 U.S.C. § 112, first paragraph, because the skilled artisan could readily make and use the claimed invention without undue experimentation. *See, e.g.*, MPEP §2164.01.

The instant specification provides extensive guidance for carrying out methods for modulating genes in cells, and particularly in cultured cells. Indeed, the Examiner concedes that the methods described in the instant specification for modulating gene expression in cultured cells meet the enablement standards of 35 U.S.C. § 112. See, Paper No. 9, page 2. As noted in Applicants' previous response, based on the knowledge of *ex vivo* strategies within the art, the skilled artisan would clearly understand and readily acknowledge that methods for manipulating gene expression in cultured cells may be used for manipulating gene expression in subjects, as contemplated by the instant claims. By disclosing one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, the instant specification satisfies the enablement requirement. *See*, MPEP § 2164.01(b) (failure to disclose other methods by which the claimed invention may be made does not render a claim invalid for lack of enablement).

Applicants respectfully submit that the Examiner, in questioning the enablement of the instant claims by attempting to minimize the understanding within the art of such *ex vivo* methods, *i.e.*, "[w]hat cell types would one use in ex vivo applications, how would one make them such that ligands delivered in vivo would enter the ex vivo delivered cells such that a modulation could be established...?" (Paper No. 9, page 6), has ignored both the teachings of the instant specification and the high level of skill in the art. Methods for introducing DNA constructs into subjects, both *in vivo* and *ex vivo*, are well known to the skilled artisan. *See, e.g.*, R.G. Crystal, page 405, right column ("Although gene transfer has not been demonstrated in all recipients, most studies have shown that genes can be transferred... whether the strategy is *ex vivo* or *in vivo*..., with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies."). Appropriately, the choice of cell type in the instant claims is left to the discretion of the skilled artisan.

With regard to how one might deliver ligands that would enter cells, the skilled artisan is well aware, and the instant specification teaches, that steroid hormones naturally exert their biological effects by entering cells and binding to hormone receptors. Thus, to argue that,

somehow, undue experimentation would be required to obtain entry of an appropriate ligand unreasonably ignores the well established biology of such ligands. Furthermore, with regard to how modulation of a gene could be established, Applicants respectfully submit that this is, in fact, a key feature of, and is extensively described by, the instant specification. Indeed, as discussed above, the Examiner concedes that the exemplary methods described in the instant specification for modulating gene expression in cultured cells meet the enablement standards of 35 U.S.C. § 112. Thus, the skilled artisan need only follow the teachings of the instant specification to establish modulation of a gene.

Therefore, Applicants respectfully submit that, whether or not certain "obstacles" might remain before gene therapy can be efficiently used in a therapeutic context, the fact remains that the skilled artisan can readily introduce DNA constructs into subjects in performance of the instantly claimed invention, using only well known methods and with only a level of experimentation typically engaged in by the artisan. *See*, MPEP § 2164.01 (the fact that experimentation may be complex does not make it undue if the art typically engages in such experimentation).

Accordingly, because the claims meet the enablement standard of 35 U.S.C. § 112, first paragraph, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

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CONCLUSION

In view of the foregoing remarks, Applicant respectfully submits that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date: 12/6/01

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Appendix A: Pending Claims

14. (Reiterated) A method for modulating the expression of an exogenous gene in a subject containing:

(i) a DNA construct encoding said exogenous gene under the control of a steroid or steroid-like hormone response element; wherein said response element is not normally present in the cells of said subject,

(ii) a receptor which is not normally present in the cells of said subject, wherein said receptor, in the presence of its associated ligand and the ultraspiracle receptor, binds to said steroid or steroid-like hormone response element, and

(iii) ultraspiracle receptor;

said method comprising administering to said subject an effective amount of said associated ligand; wherein said ligand is not normally present in the cells of said subject; and wherein said ligand is not toxic to said subject.

15. (Reiterated) A method according to Claim 14 wherein said receptor not normally present in the cells of the subject and said ultraspiracle receptor are provided to said subject by DNA construct(s) encoding said receptors.

16. (Reiterated) A method according to Claim 15 wherein said receptors are expressed under the control of a tissue specific promoter.

17. (Amended) A method according to claim 14 wherein said exogenous gene is selected from the group consisting of a gene naturally contained in the genome of said subject, and a gene not naturally contained in the genome of said subject.

18. (Reiterated) A method according to Claim 17 wherein said wild type genes are selected from genes which encode gene products:

the substantial absence of which leads to the occurrence of a non-normal state in said subject; or

a substantial excess of which leads to the occurrence of a non-normal state in said subject.

19. (Reiterated) A method according to Claim 17 wherein said therapeutic genes are selected from those which encode gene products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to said subject.

35. (Reiterated) A method of inducing the expression of an exogenous gene in a subject containing:

a) a DNA construct encoding an exogenous gene product under the control of a hormone response element; wherein said response element is not normally present in the cells of said subject,

b) DNA encoding a receptor which is not normally present in the cells of said subject, under the control of an inducible promoter; wherein said receptor, in the presence of its associated ligand and the ultraspiracle receptor, binds to said hormone response element,

c) ultraspiracle receptor, and

d) the associated ligand for said receptor which is not normally present in the cells of said subject,

said method comprising subjecting a subject to conditions suitable to induce expression of said receptor which is not normally in the cells of said subject.

36. (Reiterated) A method according to claim 35, wherein said ultraspiracle receptor is provided to said subject by a DNA construct encoding said ultraspiracle receptor.

37. (Reiterated) A method according to claim 36, wherein said receptors are expressed under the control of a tissue-specific promoter.

38. (Reiterated) A method according to claim 35, wherein said ultraspiracle receptor is substantially the same as that set forth in amino acids 1-513 of SEQ ID NO:2.

39. (Reiterated) A method according to claim 35, wherein said exogenous genes are wild type genes or therapeutic genes.

40. (Reiterated) A method according to claim 39, wherein said wild type genes encode gene products:

(a) the substantial absence of which leads to the occurrence of a non-normal state in said subject, or

(b) a substantial excess of which leads to the occurrence of a non-normal state in said subject.

41. (Reiterated) A method according to claim 39, wherein said therapeutic genes encode gene products:

(a) which are toxic to the cells in which they are expressed, or

(b) which impart a beneficial property to said subject.

42. (Reiterated) A method of inducing expression of an exogenous gene product in a subject containing a DNA construct encoding said product under the control of a hormone

response element; wherein said response element is not normally present in the cells of said subject, said method comprising introducing into said subject:

(a) a receptor which is not normally present in the cells of said subject; wherein said receptor, in combination with its associated ligand and ultraspiracle receptor, binds to said hormone response element, activating transcription therefrom,

(b) the ultraspiracle receptor, and

(c) the associated ligand for said receptor.

43. (Reiterated) A method according to claim 42, wherein said receptor not normally present in the cells of said subject and said ultraspiracle receptor are provided to said subject by DNA construct(s) encoding said receptors.

44. (Reiterated) A method according to claim 43, wherein said receptors are expressed under the control of a tissue-specific promoter.

45. (Reiterated) A method according to claim 42, wherein said ultraspiracle receptor is substantially the same as that set forth in amino acids 1-513 of SEQ ID NO:2.

46. (Reiterated) A method according to claim 42, wherein said exogenous genes are wild type genes or therapeutic genes.

47. (Reiterated) A method according to claim 46, wherein said wild type genes encode gene products:

(a) the substantial absence of which leads to the occurrence of a non-normal state in said subject, or

(b) a substantial excess of which leads to the occurrence of a non-normal state in said subject.

48. (Reiterated) A method according to claim 46, wherein said therapeutic genes encode gene products:

(a) which are toxic to the cells in which they are expressed, or

(b) which impart a beneficial property to said subject.